Central Diabetes Insipidus with Behçet's Disease

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We encountered a case of Behçet's disease complicated with central diabetes insipidus. A hypothalamopituitary dysfunction is rare in Behçet's disease; only three cases of this association have been reported in the literature. Magnetic resonance imaging of the brain showed a dilatation of the left Sylvian vein and thickening of the pituitary stalk, which suggested intracranial vasculitic processes and lymphocytic infundibuloneurohypophysitis. The possible relationship of this disease combination is discussed as a form of autoimmune disease.

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Key words: magnetic resonance imaging, pituitary gland, lymphocytic infundibuloneurohypophysitis, neuro-Behçet

Introduction

Behçet's disease is a systemic inflammatory disorder of unknown etiology. Neurological involvement is one of the most devastating manifestations of the disease, which affects the central nervous system in about 10% of Japanese patients. The brain stem is the most commonly involved in these patients (1–3). The involvement of the central nervous system includes injury of neural parenchyma and the intracranial vascular system. Central diabetes insipidus (DI) is caused by the insufficient secretion of vasopressin and manifests as polyuria and polydipsia. It is well known that part of the cause of central DI is injury of the hypothalamic-neurohypophysial system by a systemic infiltrative disease such as sarcoidosis, amyloidosis, hemochromatosis or histiocytosis X. However, to our knowledge there have been only three reports concerning hypothalamic-neurohypophysial abnormality of Behçet's disease (4–6). Here, we report a case of central diabetes insipidus complicated with Behçet's disease.

Case Report

A 40-year-old Japanese man was admitted to our hospital on Feb. 7, 1998, because of polyuria and polydipsia. He had been diagnosed with Behçet's disease in 1994 (uveitis, recurring oral and genital ulcers, skin lesions, and HLA B51 positive). Laser photocoagulation therapy was performed because of bilateral retinal neovascularization. Successful laser photocoagulation prevented complications of retinal and disc neovascularizations. The patient was treated with 1 mg of

colchicine and 3 mg of warfarin daily to prevent vein occlusion. The symptoms of Behçet's disease had been well controlled until two weeks before admission when he experienced polyuria, polydipsia and insomnia which developed gradually. He had no past history of brain tumors, trauma of the brain or infections of the central nervous system. There was no family history of Behçet's disease or diabetes insipidus. His urine volume was over 7 l per a day. The patient suffered from thirst and kept requesting cold drinks. The physical examination on admission revealed the following: height, 177 cm; weight, 61.5 kg; blood pressure, 114/79 mmHg; pulse, 83 bpm regular; temperature, 36.7°C. The examination findings of chest, abdomen and nervous system revealed no abnormalities. He had aphthous ulcers in the mouth and conjunctival dryness. The results of laboratory tests on admission are summarized in Table 1. The serum level of sodium was 153 mEq/l and osmolality was 305 mOsm/kg. His urinary gravity was under 1.005 and osmolality was 149 mOsm/kg. Endocrinological tests were normal with the exception of the plasma level of arginine vasopressin (AVP) (0.2 pg/ml). The examination of autoimmune antibodies and immunological tests revealed no abnormality. The cerebrospinal fluid showed no abnormalities. Ultrasonography of the abdomen showed no evidence of abnormal findings, such as nephrocalcinosis or hydronephrosis. The findings of the hypertonic saline infusion and subsequent pitressin loading test are shown in Fig. 1. The plasma osmolality increased sufficiently after saline infusion, however, urine osmolality and the plasma level of AVP did not increase. After intramuscular injection of pitressin, the urine was dramatically concentrated. These findings were definitive for central DI. The signal inten-

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Table 1. Laboratory Data on Admission

Hematology		Chemistry	
White blood cell count	7,700/ μ l	Sodium	<u>153 mEq/l</u>
Red blood cell count	572 $\times$ 10 ⁴ / μ l	Potassium	4.1 mEq/l
Hemoglobin	16.7 g/dl	Chloride	106 mEq/l
Hematocrit	52.5%	Calcium	10.0 mg/dl
Platelet count	201 $\times$ 10 ³ / μ l	Total protein	8.1 g/dl
		Aspartate aminotransferase	37 IU/l
ESR	4 mm/h	Alanine aminotransferase	51 IU/l
		Lactic dehydrogenase	343 IU/l
Urinalysis		Alkaline phosphatase	132 IU/l
pH	7.0	γ -Glutamyl transferase	13 IU/l
Protein	(-)	Total bilirubin	0.6 mg/dl
Occult blood	(-)	Creatine phosphokinase	96 IU/l
Sugar	(-)	Amylase	68 IU/l
Ketone	(-)	Blood urea nitrogen	9 mg/dl
Specific gravity	<u>< 1.005</u>	Creatinine	0.9 mg/dl
		Uric acid	8.7 mg/d
Arterial Blood Gas		Glucose	100 mg/dl
pH	7.383	Hemoglobin A1c	5.5%
PaO ₂	92.5 Torr	Total cholesterol	<u>255 mg/dl</u>
PaCO ₂	47.3 Torr	Triglyceride	<u>349 mg/dl</u>
HCO ₃ ⁻	27.5 mEq/l	Plasma osmolality	<u>305 mOsm/kg</u>
Saturation of oxygen	96.9%	Urine osmolality	<u>149 mOsm/kg</u>
Base excess	2.5 mEq/l		
Serology		Endocrinology	
C-reactive protein	0.15 mg/dl	Plasma AVP	<u>0.2 pg/ml</u>
Immunoglobulin G	1,237 mg/dl	Plasma ACTH	32 pg/ml
Immunoglobulin A	277 mg/dl	TSH	1.3 μ U/ml
Immunoglobulin M	172 mg/dl	Growth hormone	1.36 ng/ml
Cryoglobulin	(-)	Urinary 17-OHCS	7.9 mg/day
Rheumatoid factor	(-)	Urinary free cortisol	68 μ g/day
HBs-Antigen	(-)		
HCV-Antibody	(-)		
Autoantibody			
Anti nuclear antibody	(-)		
Anti SS-A antibody	(-)		
Anti SS-B antibody	(-)		
Anti pituitary antibody	(-)		
P-ANCA	(-)		

*underlined: abnormal data. ESR: Erythrocyte sedimentation rate, AVP: arginine vasopressin, ACTH: adrenocorticotropin, TSH: thyroid stimulating hormone, 17-OHCS: 17-hydroxycorticosteroids, P-ANCA: perinuclear antineutrophilic cytoplasmic antibodies.

sity of the posterior pituitary may reflect vasopressin content on magnetic resonance imaging (MRI) (7). T1-weighted MRI of the pituitary gland showed a decreased intensity of the posterior lobe (Fig. 2A), which is a finding compatible with central DI. A swollen pituitary stalk enhanced by gadolinium-diethylenetriamine pentaacetic acid presumably indicates inflammation of the pituitary portal system (8) (Fig. 2B). MRI of the brain also showed dilatation of the left Sylvian vein, which suggested the presence of venous thrombosis (Fig. 2C). Based on the diagnosis of central DI, we treated the patient with 10 μ g of intranasal 1-desamino-8-D-arginine vasopressin. After

the treatment, his daily urine volume decreased to 1,800 ml and his polyuria and polydipsia disappeared. The osmolality of urine and plasma were normalized and urinary gravity increased to 1.015. T1-weighted MRI of the posterior pituitary gland performed two months after the treatment showed no different findings from those before the treatment.

Discussion

The patient with Behçet's described here was diagnosed as having an unusual complication with central DI. T1-weighted

Figure 1. Hypertonic saline infusion test and pitressin loading test. After drinking 1.23 liters of water (20 ml/kg body weight) in 1 hour, the patient's urine volume was estimated every 15 minutes. When the urine volume for 15 minutes exceeded 75 ml, 370 ml of 5.0% saline was infused for 120 minutes (0.05 ml/kg/min). Although plasma osmolality (closed circle) increased sufficiently after saline infusion, the urine osmolality (open circle) and plasma level of arginine vasopressin (AVP) (closed square) did not. However, a subsequent intramuscular injection of pitressin (10 U) markedly increased urine osmolality.

MRI usually reveals the absence of a high intensity signal of the posterior pituitary of patients with DI. The findings probably reflect a decreased reserve of AVP in the posterior pituitary gland. Thus, MRI of the pathological condition with AVP hypersecretion such as nephrogenic DI or diabetes mellitus also revealed the absence of a high intensity signal of the posterior pituitary gland (9–11). Colchicine-induced nephrogenic DI has been reported (12). However, the present patient's symptoms of thirst, polyuria and polydipsia, and the volume or osmolality of the urine after the cessation of colchicine remained unchanged. This excluded the diagnosis of colchicine-induced nephrogenic DI. The absence of nephrocalcinosis or hydronephrosis, associated with possible AVP resistance, suggested that a nephrogenic origin is further unlikely. Thus, we diagnosed this case as central DI based on the hypertonic saline infusion test, low plasma AVP and the findings described above.

The uveoretinitis in our patient was treated with laser photocoagulation to prevent retinal neovascularization. Ocular complications of Behçet's disease are characterized by uveoretinitis type, retinal capillary nonperfusion, branch retinal vein occlusion, or retinal and disc neovascularization (13). The venous dilatation on the left cerebral hemisphere was thought to reflect distal venous occlusion due to probable thrombotic events. These findings suggest that Behçet's disease affects the intracranial vascular system.

Various autoantibodies are detected in lymphocytic infundibuloneurohypophysitis, leading to the speculation that it is an autoimmune disorder. Antibodies against the magnicellular neurons of the hypothalamus have been detected in some patients with central DI (14, 15), whose neurohypophysis may be affected by inflammatory infiltration (16, 17). Imura et al also suggested that lymphocytic infiltration of the infundibulum and pituitary might be a cause of idiopathic DI, and their MRI showed thickening of the pituitary stalk (7). In agreement with the report by Imura et al the pituitary MRI in the present case showed the thickening of the pituitary stalk.

Neurological manifestations of Behçet's disease may be due to injury of the central nerve parenchymal system (encephalitis, encephalomyelitis) or intracranial vascular system (cerebral venous thrombosis, intracranial aneurysms). Central DI with Behçet's disease was first reported by Hamza et al in 1989 (4). Otsuka et al also reported this combination of diseases (5). They considered that Behçet's disease could have caused hypophysitis in their case. Guma et al reported another case with the combination of central DI and Behçet's disease who showed positive perinuclear anti-neutrophilic cytoplasmic antibodies, increased lymphocytes in the cerebrospinal fluid and normal neurohypophysis examined by MRI (6). The patient reported by Guma et al had the intracranial venous dilatation as observed in the present case. They concluded that the cen-

Figure 2. Magnetic resonance imaging (MRI) view of the pituitary gland in T1-weighted images on admission showed a decreased intensity of the posterior lobe (arrow) (A). Sagittal section of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI showed a swollen pituitary stalk (arrow) (B). Coronal section of Gd-DTPA-enhanced MRI showed a dilatation of the left Sylvian vein likely caused by venous thrombosis (arrow) (C).

tral DI in their case was caused by meningeal infiltration of Behçet's disease but not by neurohypophysis. We considered neurohypophysitis to be the major cause of central DI in the present case. However, vascular involvement could not be excluded because of the presence of intracranial venous dilatation.

In conclusion, as the etiology of Behçet's disease is considered an autoimmune disease, it could have caused neurohypophysitis. The possible relationship of this disease combination may be interpreted in the context of infundibuloneurohypophysitis due to an autoimmune process.

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